

1. (Original) A method for selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDK1), the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDK1, wherein a three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound, and a compound that is predicted to interact with the said protein kinase catalytic domain is selected, wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 is a three-dimensional structure (or part thereof) determined for a polypeptide consisting of residues equivalent to residues 51 to 359 of full length human PDK1, or a fragment or fusion thereof.

2. (Original) The method of claim 1 wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 structure is a three-dimensional structure (or part thereof) determined for a polypeptide consisting of residues 51 to 359 of full length human PDK1 or a fusion thereof.

3. (Original) The method of claim 2 wherein the three-dimensional structure (or part thereof) is determined for a polypeptide consisting of residues 51 to 359 of full length human PDK1 and the amino acid sequence Gly-Pro preceding the methionine corresponding to Met51 of human PDK1.

4. (Original) The method of claim 1 wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 structure is a three-dimensional

structure (or part thereof) determined for a polypeptide consisting of residues 71 to 359 of full length human PDK1 or a fusion thereof.

5. (Currently Amended) The method of ~~any one of the preceding claims~~ claim 1 wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 structure is obtainable by X-ray analysis of a crystal obtainable using a mother liquor solution comprising ammonium sulphate.

6. (Original) The method of claim 5 wherein the mother liquor solution is of pH 7 to 9.

7. (Original) The method of claim 6 wherein the mother liquor solution is of pH 8.5.

8. (Currently Amended) The method of ~~any one of claims 5 to 7~~ claim 7 wherein the mother liquor solution comprises ATP.

9. (Currently Amended) The method of ~~any one of claims 1 to 3, 5 to 8~~ claim 1 wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 structure is that represented by the structure co-ordinates shown in Examples 2, 3 or 4, or 7 or 8, or a structure modelled on such structure co-ordinates.

10. (Currently Amended) The method of ~~any one of the preceding claims~~ claim 1 wherein the molecule is predicted to bind to a region of the structure termed the "PIF binding pocket" (formed by residues including residues Lys115, Ile118, Ile119 on the α B helix, Val124, Val127 on the α C helix and Leu 155 on β -sheet 5 of full length human PDK1, or equivalent

residues), the "phosphate binding pocket" (formed by residues including residues Lys76, Arg 131, Thr 148 and Gln150 of full length human PDK1, or equivalent residues) and/or the α C helix (residues equivalent to 123-136 of full length human PDK1), or interacting regions.

11. (Currently Amended) The method of ~~any of the preceding claims~~ claim 1 wherein the compound is for modulating the protein kinase activity of PDK1 towards PKB or other PH-domain-comprising/phosphoinositide-binding substrate of PDK1.

12. (Currently Amended) The method of ~~any one of claims claim 1 to 10~~ wherein the compound is for modulating the protein kinase activity of PDK1 towards SGK, S6K or other substrate of PDK1 whose phosphorylation by PDK1 is promoted by phosphorylation of the substrate on the Ser/Thr of the "hydrophobic motif" FXXFS/TY.

13. (Original) A method for selecting or designing a compound for modulating the activity of a hydrophobic pocket (PIF binding pocket)-containing protein kinase having a hydrophobic pocket in the position equivalent to the hydrophobic pocket of human PDK1 that is defined by residues including Lys115, Ile118, Ile119, Val124, Val127 and/or Leu155 of full-length human PDK1 and further having a phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by residues including Lys76, Arg131, Thr148 and/or Gln150, the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the said hydrophobic pocket-containing protein kinase, wherein a three-dimensional structure of a compound is compared with a

three-dimensional structure of the said phosphate binding pocket and optionally also the hydrophobic pocket and/or α C helix or region interacting therewith, and a compound that is predicted to interact with the said phosphate binding pocket and optionally also the hydrophobic pocket and/or α C helix or region interacting therewith, is selected.

14. (Original) The method of claim 13 wherein the protein kinase is an isoform of Serum and Glucocorticoid stimulated protein kinase (SGK), Protein Kinase B (PKB), p70 S6 kinase, p90 RSK, PKC isoforms (for example PKC α , PKC δ , PKC ζ), PRK1, PRK2, MSK1 or MSK2.

15. (Currently Amended) The method of claim 13 ~~or 14~~ wherein the three-dimensional structure of ~~the~~ said phosphate binding pocket and optionally also the hydrophobic pocket and/or α C helix or region interacting therewith is a structure modelled on the basis of a three-dimensional structure as defined in ~~any one of claims 1 to~~ claim 9.

16. (Currently amended) The method of ~~any one of the preceding claims~~ claim 1 further comprising the step of synthesising, purifying and/or formulating the compound.

17. (Original) A method for assessing the activation state of a structure for a protein kinase, wherein the structure is analysed using principle component analysis of the structure co-ordinates.

18. (Original) The method of claim 17 wherein the activation state of the structure is classified as "open", "closed" or "intermediate".

19. (Original) A mutated protein kinase, wherein the protein kinase before mutation has a hydrophobic pocket in the position equivalent to the hydrophobic pocket (PIF-binding pocket) of human PDK1 that is defined by residues including Lys115, Ile118, Ile119, Val124, Val127 and/or Leu155 of full-length human PDK1 and further has a phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by residues including Lys76, Arg131, Thr148 and/or Gln150, and wherein one or more residues equivalent to Ile118, Val124, Val127, Lys76 or Thr148 forming part of the hydrophobic pocket or phosphate binding pocket of the protein kinase is mutated.

20. (Original) The mutated protein kinase of claim 19 wherein the protein kinase is PDK1.

21. (Original) The mutated protein kinase of claim 19 wherein the protein kinase is SGK, PKB or p70 S6 kinase.

22. (Currently amended) The mutated protein kinase of ~~any one of claims~~ claim 19 ~~to 21~~ wherein the residue at the position equivalent to residue Lys76 of PDK1 is mutated to an Ala.

23. (Currently amended) A polynucleotide encoding a mutated protein kinase according to ~~any one of claims~~ claim 19 ~~to 22~~.

24. (Currently amended) A polynucleotide according to claim 23 suitable for expressing a mutated protein kinase according to ~~any one of claims~~ claim 19 ~~to 22~~.

25. (Currently amended) A host cell comprising a polynucleotide according to claim 23 ~~or 24~~.

26. (Currently amended) A method of making a mutated protein kinase according to ~~any one of claims~~ claim 19 to 22, the method comprising culturing a host cell according to claim 25 which expresses said mutated protein kinase and isolating said mutated protein kinase.

27. (Canceled)

28. (Currently amended) A method of identifying a compound that modulates the protein kinase activity of a protein kinase as defined in claim 19 (for example PDK1), comprising the step of determining the effect of the compound on the protein kinase activity of, or ability of the compound to bind to a mutated protein kinase according to ~~any one of claims~~ claim 19 to 22, 27.

29. (Currently amended) The method of claim 28 further comprising the step of determining the effect of the compound on the protein kinase activity of, or ability of the compound to bind to, the protein kinase (for example PDK1) which is not mutated as defined in ~~any one of claims~~ claim 19 to 22.

30. (Original) An antibody reactive with the phosphate binding pocket of PDK1 or other protein kinase as defined in claim 19; or an antibody reactive with PDK1 or other protein kinase as defined in claim 19 but not with the said protein kinase mutated at the phosphate binding site, or vice versa..

31. (Original) A method for preparing or selecting an antibody according to claim 30 wherein the antibody is prepared or selected against a said protein kinase (for

example PDK1) unmutated at the phosphate binding site and a said protein kinase mutated at the phosphate binding site.

32. (Currently amended) A kit of parts comprising (1) a mutated protein kinase (for example mutated PDK1) according to ~~any one of claims claim 19 to 22, 27~~ (2) the corresponding protein kinase (for example PDK1) which is not mutated as defined in ~~any one of claims claim 19 to 22~~.

33. (Original) A compound identified or identifiable by ~~any one of claims claim 1 to 16, 28 or 29~~.

34. (Currently amended) The compound of claim 33 wherein the compound comprises an antibody or RNA molecule.

35. Canceled

36. (Currently amended) ~~Use of a compound, mutated protein kinase or polynucleotide as defined in claim 35 in the manufacture of a~~ A medicament for the treatment of a patient in need of modulation of signalling by a protein kinase as defined in claim 19, for example PDK1, SGK, PKB or p70 S6 kinase, for example insulin signalling pathway and/or PDK1/PDK2/SGK/PKB/p70 S6 kinase/PRK2/PKC signalling.

37. (Currently amended) A method of treating a patient in need of modulation of signalling by a protein kinase as defined in claim 19, for example PDK1, SGK, PKB or p70 S6 kinase, for example insulin signalling pathway and/or PDK1/PDK2/SGK/PKB/p70 S6 kinase/PRK2/PKC signalling, wherein the patient is administered an effective amount of a compound, mutated protein kinase or polynucleotide ~~as defined in claim 35~~.

38. (Currently amended) A crystalline form of a polypeptide consisting of residues 51 to 359 of full length human PDK1 or a fusion thereof ~~as defined in any one of claims 1 to 4.~~

39. (Original) The crystalline form of claim 38 wherein the crystalline form further comprises co-crystallised molecule.

40. (Original) The crystalline form of claim 39 wherein the co-crystallised molecule modulates protein kinase activity.

41. (Original) The crystalline form of claim 40 wherein the co-crystallised molecule modulates PDK1 protein kinase activity.

42. The crystalline form of ~~any one of claims~~ claim 39 ~~to 41~~ wherein the co-crystallised molecule is staurosporine, the staurosporine derivative UCN-01 (7-hydroxyl staurosporine) or other staurosporine derivative.

Respectfully submitted,

December 8, 2004
Date

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